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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,200	04/03/2001	Douglas A. Russell	18337.006	5401

7590 10/20/2003

ARNOLD & PORTER
Attn: IP Docketing Department Room 1126B
555 - 12th Street NW
Washington, DC 20004-1206

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/824,200	RUSSELL ET AL.	
	Examin r	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13,20,22 and 91-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13,20,22 and 91-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2003 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-7, 9, 10, 20 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baszczynski et al (U.S. Patent 5,767,379) in view of Ganz et al (Transgenic plants pp. 281-97) and further in view of Brar et al (WO 98/10062).

Baszczynski teaches a method for producing a protein in the seed of a corn plant (see column 11, table 1 and column 10, lines 1-49) comprising the steps:

(a) cultivating said transformed corn plant under the appropriate conditions to result in the expression of said protein in the seed of said corn plant (see column 11, example 2 and tables 1 and 2)

(b) wherein said protein accumulates to a level greater than 1% of the total soluble protein in a sample of the seed of the corn plant (see column 9, line 66 to column 10, line 2, where Baszczynski states "It is apparent from the above discussed data that avidin from corn seed of transgenic plants within the present invention can be produced at a high level, over 1% of avidin per total extracted protein."

With regard to claim 2, Baszczynski teaches purification (see column 11, table 1)

With regard to claims 3-5, 91-93, Baszczynski teaches "Furthermore, avidin extended from maize is structurally and functionally indistinguishable from avidin extracted from chicken egg white (see column 10, lines 2-4)" which expressly teaches that there is no addition of other modifications such as glycosylation to the protein.

With regard to claims 6, 7, 9, and 10, Baszczynski teaches the maize ubiquitin promoter (see column 3, lines 58-59) operably linked to the barley alpha amylase signal sequence (see column 3, lines 45-47) which is linked in frame to the avidin protein

sequence (see column 3, lines 45-50) which is fused to a transcription termination sequence (see column 3, lines 61-62).

Baszczynski does not teach expression of cytokines in the corn plants.

Ganz teaches expression of cytokines including GM-CSF in plants (see page 287-289, for example).

Brar teaches expression of antibodies in corn at ranges from 0.4 to 10% of total soluble protein (see page 28, lines 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to express cytokines in corn plants using the method of Baszczynski since Baszczynski states "It is also feasible to express in plants heterologous genes expressing high value products. In many cases, expression in plants could be the system of choice, because of such inherent advantages such as cost relative to that of tissue culture and concern about correct glycosylation and other post-translational processing of the expression product from other expression systems (see column 1, lines 33-38)". Baszczynski further motivates the invention by noting that "It is apparent from the above discussed data that avidin from corn seed of transgenic plants within the present invention can be produced at a high level, over 1% of avidin per total extracted protein. (see column 9, line 66 to column 10, line 2)."

Further motivation to specifically express cytokines at these high levels in transgenic corn plants as taught by Baszczynski is provided by Ganz, who states "The demand for these growth factors is expected to increase exponentially as additional clinical benefits are discovered. At the same time, there is no doubt that the high cost of

recombinant EP and GM-CSF is an impediment to their expanded use (see page 284, column 2)." Ganz continues on the same page to note the advantages of expression of the cytokines in plants, stating "The production of recombinant proteins in plant expression systems has many potential advantages for generating biopharmaceuticals relevant to clinical medicine. These include the following: (i) plant systems are more economical than industrial facilities using mammalian expression systems; (ii) technology is extant for harvesting and processing plants/plant products on a large scale; (iii) proteins are post-translationally modified similar to mammalian systems (e.g. see table 7-4.1); (iv) plants can be directed to secrete proteins into stable, dry intracellular compartments of seeds called endosperm protein bodies, which can be easily collected; (v) the amount of recombinant product that can be produced approaches industrial scale levels; and (vi) health risks due to contamination with potential pathogens/toxins are minimized (see page 284, last paragraph to page 285, top paragraph)."

With regard to the issue of reasonable expectation of success in producing corn plants which express cytokines at levels of 1% of total soluble proteins, each reference cited shows expression levels of 1% or greater. Baszczynski states "It is apparent from the above discussed data that avidin from corn seed of transgenic plants within the present invention can be produced at a high level, over 1% of avidin per total extracted protein. (see column 9, line 66 to column 10, line 2)." Brar actually claims expression levels ranging from 1% to 10% of total soluble proteins (see page 36, claims 13-16) and demonstrates expression of 1.6% to 12.8% of total soluble protein in corn seeds (see

page 28, line 27). Finally, Ganz provides evidence that cytokines can be expressed in plant cells (see page 289, figure 7-4.4). Therefore, there is a reasonable expectation of success in expressing cytokines in corn at levels of over 1% of soluble protein since both Baszczynski and Brar exceeded that level of expression of heterologous proteins in corn.

5. Claim 1-7, 9, 10, 13, 20, 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (U.S. Patent 6,020,169) in view of Baszczynski et al (U.S. Patent 5,767,379) and further in view of Brar et al (WO 98/10062).

Lee teaches a method for producing a cytokine, such as IL-4, which is free from amino acid modifications or novel glycosylation (see figure 13 which shows that IL-4 has same molecular weight as recombinant human IL-4) in a plant host system wherein said plant host system has been transformed with a chimeric nucleic acid sequence encoding said cytokine (see column 6, lines 6-21 and column 20, lines 15-67) comprising the steps:

(a) cultivating said transformed plant host system under the appropriate conditions to result in the expression of said cytokine in said plant host system (see column 20, lines 15-67)

(b) wherein Lee also expressly teaches that expression of over 1% of total protein is achievable (see column 1, line 45).

Lee purifies the cytokine using SDS-PAGE and TCA precipitation (see column 21, lines 7-16).

Lee teaches a chimeric nucleic acid molecule which comprises the cloned plant cytokine gene (see column 9, lines 58-60) under the control of a plant promoter sequence (see column 9, line 60 to column 10, line 2) as well as signal sequences including signal sequences to the endoplasmic reticulum (see column 5, line 51 to column 6, line 5).

Lee teaches expression of GM-CSF (see column 22, example 4).

Lee does not teach expression in corn plants and while Lee states that 1% expression is achievable, applicant here contends that Lee did not demonstrate such expression.

Baszczynski teaches a method for producing a protein in the seed of a corn plant (see column 11, table 1 and column 10, lines 1-49) wherein said protein accumulates to a level greater than 1% of the total soluble protein in a sample of the seed of the corn plant (see column 9, line 66 to column 10, line 2, where Baszczynski states "It is apparent from the above discussed data that avidin from corn seed of transgenic plants within the present invention can be produced at a high level, over 1% of avidin per total extracted protein."

Brar teaches expression of antibodies in corn at ranges from 0.4 to 10% of total soluble protein (see page 28, lines 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to express cytokines as taught by Lee in corn plants using the method of Baszczynski since Baszczynski states "It is also feasible to express in plants heterologous genes expressing high value products. In many cases, expression

in plants could be the system of choice, because of such inherent advantages such as cost relative to that of tissue culture and concern about correct glycosylation and other post-translational processing of the expression product from other expression systems (see column 1, lines 33-38)". Baszczynski further motivates the invention by noting that "It is apparent from the above discussed data that avidin from corn seed of transgenic plants within the present invention can be produced at a high level, over 1% of avidin per total extracted protein. (see column 9, line 66 to column 10, line 2)." An ordinary practitioner would have been motivated to express cytokines in corn as taught by Baszczynski in order to achieve the expected advantages of cost advantages as well as the high level of expression shown by both Baszczynski and Brar.

With regard to the issue of reasonable expectation of success in producing corn plants which express cytokines at levels of 1% of total soluble proteins, each reference cited shows expression levels of 1% or greater. Baszczynski states "It is apparent from the above discussed data that avidin from corn seed of transgenic plants within the present invention can be produced at a high level, over 1% of avidin per total extracted protein. (see column 9, line 66 to column 10, line 2)." Brar actually claims expression levels ranging from 1% to 10% of total soluble proteins (see page 36, claims 13-16) and demonstrates expression of 1.6% to 12.8% of total soluble protein in corn seeds (see page 28, line 27). Finally, Lee provides evidence that cytokines can be expressed in plant cells (see figure 11,). Therefore, there is a reasonable expectation of success in expressing cytokines in corn at levels of over 1% of soluble protein since both

Baszczynski and Brar exceeded that level of expression of heterologous proteins in corn.

6. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baszczynski et al (U.S. Patent 5,767,379) in view of Ganz et al (Transgenic plants pp. 281-97) and further in view of Brar et al (WO 98/10062) and further in view of Boone et al (U.S. Patent 5,849,883).

Baszczynski in view of Ganz and further in view of Brar teach the limitations of claims 1-7, 9, 10, 20 and 91-93 as discussed above. Baszczynski in view of Ganz and further in view of Brar do not teach expression of G-CSF.

Boone suggests expression of G-CSF in plants (see column 10, line 9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to express G-CSF in plants using the method of Baszczynski in view of Ganz and further in view of Brar since Boone expressly teaches that the G-CSF polypeptides can be the product of "prokaryotic or eukaryotic host expression (e.g. by bacterial, yeast, higher plant, insect and mammalian cells in culture)(see column 10, lines 6-9)". An ordinary practitioner, taught by Baszczynski in view of Ganz and further in view of Brar a method which teaches expression of over 1% of soluble protein in corn plants would have been motivated to apply this high level gene expression method to express the G-CSF of Boone since Boone expressly suggests plant cell expression of the protein. Further an ordinary practitioner would have been motivated in order to get more protein.

7. Claims 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baszczynski in view of Ganz and further in view of Brar in view of Schouten et al (FEBS Lett. (1997) 415:235-241).

Baszczynski in view of Ganz and further in view of Brar teach the limitations of claims 1-7, 9, 10, 20 and 91-93 as discussed above. Baszczynski in view of Ganz and further in view of Brar do not teach the use of KDEL sequence at the 3' end of the sequence.

Schouten teaches the use of a KDEL sequence at the 3' end of proteins for ER expression (see abstract, page 235, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the KDEL sequence of Schouten in the cytokine expression method of Baszczynski in view of Ganz and further in view of Brar since Schouten states "It was unexpectedly shown that addition at the C-terminus of the ER retention signal KDEL resulted in significantly improved expression levels (abstract)". An ordinary practitioner would have been motivated to use the KDEL retention signal of Schouten in the expression method of Baszczynski in view of Ganz and further in view of Brar in order to achieve significantly improved expression levels, since more protein is the desired result by any ordinary practitioner.

8. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (U.S. Patent 6,020,169) in view of Baszczynski et al (U.S. Patent 5,767,379) and further in view of Brar et al (WO 98/10062) and further in view of Boone et al (U.S. Patent 5,849,883).

Lee in view of Baszczynski and further in view of Brar teach the limitations of claims 1-7, 9, 10, 13, 20 and 91-93 as discussed above. Lee in view of Baszczynski and further in view of Brar do not teach expression of G-CSF.

Boone suggests expression of G-CSF in plants (see column 10, line 9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to express G-CSF in plants using the method of Lee in view of Baszczynski and further in view of Brar since Boone expressly teaches that the G-CSF polypeptides can be the product of "prokaryotic or eukaryotic host expression (e.g. by bacterial, yeast, higher plant, insect and mammalian cells in culture)(see column 10, lines 6-9)". An ordinary practitioner, taught by Lee in view of Baszczynski and further in view of Brar a method which teaches expression of over 1% of soluble protein in corn plants and which teaches expression of cytokines would have been motivated to apply this high level gene expression method to express the G-CSF of Boone since Boone expressly suggests plant cell expression of the protein. Further an ordinary practitioner would have been motivated in order to get more protein.

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee in view of Baszczynski and further in view of Brar in view of Schouten et al (FEBS Lett. (1997) 415:235-241).

Lee in view of Baszczynski and further in view of Brar teach the limitations of claims 1-7, 9, 10, 13, 20 and 91-93 as discussed above. Lee in view of Baszczynski and further in view of Brar do not teach the use of KDEL sequence at the 3' end of the sequence.

Schouten teaches the use of a KDEL sequence at the 3' end of proteins for ER expression (see abstract, page 235, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the KDEL sequence of Schouten in the cytokine expression method of Lee in view of Baszczynski and further in view of Brar since Schouten states "It was unexpectedly shown that addition at the C-terminus of the ER retention signal KDEL resulted in significantly improved expression levels (abstract)". An ordinary practitioner would have been motivated to use the KDEL retention signal of Schouten in the expression method of Baszczynski in view of Ganz and further in view of Brar in order to achieve significantly improved expression levels, since more protein is the desired result by any ordinary practitioner.

Response to Arguments

10. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634